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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/585,417	04/10/2007	Kenji Miyamoto	Q95907	4711

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EXAMINER	
GOON, SCARLETT Y	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/585,417	MIYAMOTO ET AL.	
	Examiner	Art Unit	
	SCARLETT GOON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *28-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7 July 2006 and 10 April 2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-35 are pending in the instant application.

Priority

This application is a National Stage entry of PCT/JP05/00125 filed on 7 January 2005 and claims priority to Japan foreign application 2004-002478 filed on 7 January 2004. A certified copy of the foreign priority document in Japanese has been received. No English translation has been received.

Information Disclosure Statement

The information disclosure statements (IDS) dated 7 July 2006 and 10 April 2007 comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609, except where noted. Accordingly, they have been placed in the application file and the information therein has been considered as to the merits.

The foreign documents cited on the IDS dated 7 July 2006 were not considered because copies of the documents and translations, if relevant, were not provided to the Office.

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-27, drawn to a hyaluronic acid derivative in which an anti-inflammatory drug is bound to hyaluronic acid through a covalent bond via a spacer having a biodegradable region, in the reply filed

on 29 December 2008 is acknowledged. In response to a requirement for a species election, Applicants elect (i) a non-steroidal anti-inflammatory drug, (ii) diclofenac; and (iii) the compound of Formula (1) wherein Y-CO- is hyaluronic acid, R^1 is a linear hydrocarbon group having two carbon atoms which may have a substituent, R^2 is a non-steroidal anti-inflammatory drug residue represented by Formula (2) and n is an integer of from 1 to 3; and for Formula (2), R^3 is diclofenac, R^4 and R^5 each represent a hydrogen atom, and X represents a chlorine atom.

Claims 28-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 29 December 2008.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-27 will be examined on its merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 and 12-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation "hyaluronic acid derivative" renders the claims herein indefinite. The recitation of a "derivative" is not clearly defined in the specification, and therefore does not set forth the metes and bounds of the term "derivative". The Merriam-Webster's Online Dictionary defines "derivative" as "a chemical substance related structurally to another substance and theoretically derivable from it" (PTO-892, Ref. U). Hence, one of ordinary skill in the art could not ascertain and interpret the metes and bounds of the patent protection desired as to "hyaluronic acid derivative" herein. Thus, it is unclear and indefinite as to how the "derivative" herein is encompassed thereby.

35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 and 12-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are directed to a hyaluronic acid derivative in which an anti-inflammatory drug is bound to hyaluronic acid through a covalent bond via a spacer having a biodegradable region.

The MPEP states that for a generic claim, the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. See MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad genus. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618. Furthermore, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.,* 43 USPQ2d 1398.

Additionally, in *Carnegie Mellon University v. Hoffman-La Roche Inc.*, Nos. 07-1266, -1267 (Fed. Cir. Sept. 8, 2008), the Federal Circuit affirmed that a claim to a genus described in functional terms was not supported by the specification's disclosure of species that were not representative of the entire genus.

The claims are rejected under the written description requirement for failing to disclose a representative number of species for the claimed genus.

The Guidelines for Examination of Patent Applications under the 35 USC § 112, first paragraph, "Written Description" Requirement", published at Federal Register, Vol. 66, No. 4, pp. 1099-1111 outline the method of analysis of claims to determine whether adequate written description is present. The first step is to determine what the claim as a whole covers, i.e., discussion of the full scope of the claim. Second, the application should be fully reviewed to understand how applicant provides support for the claimed invention including each element and/or step, i.e., compare the scope of the claim with the scope of the description. Third, determine whether the applicant was in possession of the claimed invention as a whole at the time of filing. This should include the following considerations: (1) actual reduction to practice, (2) disclosure of drawings or structural chemical formulas, (3) sufficient relevant identifying characteristics such as complete structure, partial structure, physical and/or chemical properties and functional characteristics when coupled with a known or disclosed correlation between function and structure, (4) method of making the claimed invention, (5) level of skill and knowledge in the art and (6) predictability of the art. For claims 1-9 and 12-27, each of these factors has been considered, with the most relevant factors discussed below. For each claim drawn to a genus, each of these factors is to be considered to determine whether there is disclosure of a representative number of species that would lead one skilled in the art to conclude that applicant was in possession of the claimed invention. Where skill and knowledge in the art is high, adequate written description would require fewer species to be disclosed than in an art where little is known; further, more species

would need to be disclosed to provide adequate written description for a highly variable genus.

First, what do the claims as a whole cover? Claim 1 and dependent therefrom are directed to a hyaluronic acid derivative in which an anti-inflammatory drug is bound to hyaluronic acid through a covalent bond via a spacer having a biodegradable region. Dependent claims 2-9 and 12-27 further limit the genus of the claimed compounds.

Second, how does the scope of the claims compare to the scope of the disclosure? The recitations "anti-inflammatory drug," "non-steroidal anti-inflammatory drug," and "spacer," are claimed broader than what is supported in the disclosure. The specification only provides a very limited subset of species for such claimed genus of compounds.

Third, the factors need to be considered, with the most relevant factors discussed below.

Reduction to Practice: The only anti-inflammatory drugs reduced to practice are non-steroidal anti-inflammatory drugs that include ketoprofen, naproxen, ibuprofen, flurbiprofen, acetylsalicylic acid, felbinac, fenbufen, mefenamic acid, diclofenac, etodolac and actarit. The only spacers reduced to practice are aminopropanol, 2-amino-1,5-pentanediol, serinol, 3-amino-1,2-propanediol, aminoethanol, diaminopropane, and tris(hydroxymethyl)aminomethane.

Disclosure of Drawings or Structural Chemical Formulas: The only disclosure, in addition to the species reduced to practice, is in the form of lists of other possible species of anti-inflammatory drugs, as well as a disclosed sub-genus of spacers which

are compounds selected from the group consisting of diaminoalkanes having from 2 to 18 carbon atoms, an aminoalkyl alcohol having from 2 to 12 carbon atoms and an amino acid. The recitations "anti-inflammatory drug," "non-steroidal anti-inflammatory drug," and "spacer," are seen to be merely functional language. Functional language at the point of novelty, as herein employed by Applicants, is admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC, 1997) at 1406: stating this usage does "little more than outline goal appellants hope the recited invention achieves and the problems the invention will hopefully ameliorate". The CAFC further clearly states that "A definition by function, as we have previously indicated, does not suffice to define the genus…" at 1406 (emphases added).

Method of Making the Claimed Invention: The disclosure provides extensive examples for the synthesis of a hyaluronic acid conjugate linked to specific non-steroidal anti-inflammatory drugs, which contain carboxyl groups, via spacers that are diaminoalkanes and aminoalkyl alcohols, as well one example for the synthesis of conjugates wherein the linker is serinol. However, there is no disclosure for the synthesis of conjugates that comprise spacers with other functional groups, such as aminooxy groups, thiols, and hydrazides. Additionally, there is no disclosure for the synthesis of conjugates wherein the anti-inflammatory drug is anything but a non-steroidal anti-inflammatory drug and wherein the non-steroidal anti-inflammatory drug does not contain a carboxyl group.

Level of Skill in the Art and Knowledge in the Art: The level of skill in the art is low.

Thus, having analyzed the claims with regard to the Written Description guidelines, it is clear that Applicant's functional language at the points of novelty fails to meet the requirements set forth under 35 U.S.C. 112, first paragraph. Claims employing functional language at the exact point of novelty, such as Applicant's, neither provide those elements required to practice the inventions, nor "inform the public during the life of the patent of the limited monopoly asserted" (*General Electric Company v. Wabash Appliance Corporation et al.* 37 USPQ at 468 (US Supreme Court 1938)). Thus, one skilled in the art would be lead to conclude that Applicant was not in possession of the claimed invention at the time the application was filed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5-7 and 19-23 are rejected under 35 U.S.C. 102(b) as being anticipated by EP 1082963 A1 to Tamura *et al.* (PTO-892, Ref. N).

Tamura *et al.* disclose a conjugate of hyaluronic acid and a therapeutic agent for treatment of joint diseases. The therapeutic agent is effective for treating osteoarthritis, rheumatoid arthritis and the like (paragraph 0001). The therapeutic agent for joint diseases includes non-steroidal anti-inflammatory agents, cyclooxygenase-2 inhibitors, antirheumatic agents, steroids, local anesthetics, and cartilage protective agents

(paragraph 0034). Non-steroidal anti-inflammatory agents include, for example, salicylic acid based agents, fenamic acid based agents, arylacetic acid based agents, propionic abid based agents, pyrazolone based agents, and oxicam based agents (paragraph 0034). The bond between the therapeutic agent for joint diseases and hyaluronic acid is a covalent bond (paragraph 0021). Chemical conjugation of hyaluronic acid with the therapeutic agent for joint diseases can occur via reaction at the carboxyl group, the hydroxyl group, or the aldehyde group originating from the reducing end of hyaluronic acid (paragraph 0072). The linkage between hyaluronic acid and the therapeutic agent can occur via a spacer (paragraph 0023). The type of spacers is not limited unless the activities of the therapeutic agent for joint diseases and the hyaluronic acid are materially affected (paragraph 0060). Spacers exemplified by Tamura *et al.* include C_4H_8NH- and $C_8H_{16}NH$- in conjugates 1 and 3 (p. 19, Table 1), which were synthesized from 1,4-diaminobutane (paragraph 0088) and 1,8-diaminooctane (paragraph 0093), respectively. The hyaluronic acid has a weight average molecular weight of 100,000 to 10,000,000 and is composed of glucuronic acid and N-acetylglucosamine (paragraph 0050). From the standpoint of the strength in viscoelasticity, hyaluronic acid having a weight average molecular weight of 700,000 to 10,000,000 is preferred. If the hyaluronic acid-therapeutic agent conjugate is to be used as a drug, it is preferably used after being formulated into a pharmaceutical preparation together with a pharmaceutically acceptable diluting agent, stabilizer and the like (paragraph 0085). The mode of administration of the drug or pharmaceutical composition is not particularly limited and may be oral or parenteral and may be systemic or local. In general, it is

preferably administered parenterally and locally, for example, intraarticularly, intravenously, intramuscularly or intradermally as injection, or percutaneously as a spraying agent, a topical cream or an ointment (paragraph 0086).

Applicants are requested to note that although the limitations "that the pharmaceutical agent is an arthritis-treating agent, an anti-inflammatory medicament or an analgesic," that it "is useful for parenteral administration," "is an injection useful for topical administration" or "is an injection useful for intra-articular administration" is disclosed by Tamura *et al.*, these recitations are considered to be an "intended use" of the composition, and is therefore not given any patentable weight. Applicant is requested to note that the "intended use" of a composition will not further limit the claims drawn to a composition or product, so long as the prior art discloses the same composition comprising the same ingredients in an effective amount, as the instantly claimed. See, e.g., *Ex parte Masham*, 2 USPQ2d 1647 (1987) and *In re Hack* 114, USPQ 161.

Thus, the conjugate comprising hyaluronic acid linked to a non-steroidal anti-inflammatory agent via a diamino linker, disclosed by Tamura *et al.*, anticipates instant claims 1-3, 5-7 and 19-23.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 1082963 A1 to Tamura *et al.* (PTO-892, Ref. N), in view of JP 9-188705 to Miyamoto *et al.* (PTO-892, Ref. O, machine translation).

The teachings of Tamura *et al.* were as disclosed above in the claim rejections under 35 USC § 102. Tamura *et al.* further teach diclofenac sodium salt, tolmetin sodium salt, sulindac, fenbufen, indomethacin, acemetacin, among others, as examples

of arylacetic acid based non-steroidal anti-inflammatory agents that can be used for conjugation to hyaluronic acid (paragraph 0034). Using cartilage protective agents, in particular matrix metalloprotease inhibitors, as an example of a therapeutic agent for joint disease that can be conjugated to hyaluronic acid, Tamura *et al.* teach that the weight ratio of the matrix metalloprotease inhibitor to the entire conjugate is preferably 0.01 to 50%, more preferably 0.1 to 10%, although the weight ratio is not particularly limited (paragraph 0024).

Although Tamura *et al.* teach the use of various diamino alkyl compounds as spacers in the hyaluronic acid-therapeutic agent conjugate, Tamura *et al.* do not teach the use of a spacer shorter than 1,4-diaminobutane.

Miyamoto *et al.* teach glycosaminoglycan derivatives containing a carboxylic acid, a hydroxyl group, or an amino group which is introduced onto the glycosaminoglycan by way of a spacer. The spacer can be a diamine compound or an amino acid which forms a covalent bond with a carboxylic acid present on the glycosaminoglycan to give an amide bond (claim 7; paragraph 0032). The glycosaminoglycan is useful for improving the stability of peptides, proteins, and other drugs in the living body (paragraph 0002). Glycosaminoglycans of particular interest include chondroitin sulfate and hyaluronic acid, which are useful for the treatment of arthritis (paragraph 0002). Though the molecular weight of the glycosaminoglycan is not limiting, it is preferable that it be about 10,000-5,000,000 Da, more preferably about 20,000-2,000,000 (paragraph 0014). Examples of drugs that can be conjugated to the glycosaminoglycan include those which contain a carboxylic acid group such

indomethacin, deoxycholic acid, acetylsalicylate, salazosulfapyridine, methotrexate, and leucine enkephalin (claim 7), which can be reacted with the glycosaminoglycan derivative at the amino group of the spacer (paragraph 0009). When a diamino compound is used as the spacer, they can be represented by H_2N-$(CH_2)_n$-NH_2 wherein n is preferably 2-18 (paragraph 0031). An example is provided wherein hyaluronic acid is modified with 1,6-hexanediamine at a 56% introduction of the spacer (paragraph 0042). Another example is provided wherein chondroitin sulfate is modified with 1,6-hexanediamine at a 32% introduction of the spacer (paragraph 0038). The amino-modified chondroitin sulfate was then further conjugated to deoxycholic acid with a 27% introductory rate (paragraph 0039). Additionally, an example is provided wherein hyaluronic acid with an average molecular weight of 40,000 is conjugated to salazosulfapyridine at a 5% introduction of the drug (paragraph 0044). In the working examples taught by Miyamoto *et al.*, the glycosaminoglycan derivatives and/or conjugates were precipitated by ethanol, dialyzed in deionized water, filtered through a 0.22 micron filter, and then freeze-dried (paragraph 0039 and 0042).

Applicants are requested to note that the recitations "wherein a solution obtained by dissolving the hyaluronic acid derivative in an aqueous medium to a concentration of 1.0% by weight is capable of passing through a porous filter having a pore size of 0.45 μm and a diameter of 25 mm, at a ratio of 2 mL per minute or more at a temperature of 24 C under pressure of 5.0 kg/cm^2" and "wherein a solution obtained by dissolving the hyaluronic acid derivative in an aqueous medium to a concentration of 1.0% by weight is capable of passing through a porous filter having a pore size of 0.22 μm and a

diameter of 25 mm, at a ratio of 2 mL per minute or more at a temperature of 24 C under pressure of 5.0 kg/cm^2" in claims 14 and 15, respectively, and the recitation "which is capable of being pushed out from an injector" in claims 16 and 24, are considered to merely state the results of the limitations in the claim. Thus, it adds nothing to the patentability or substance of the claim. When, as here, the prior art appears to contain the exact same ingredients and applicant's own disclosure supports the suitability of the prior art composition as the inventive composition component, the burden is on the applicant to show a novel or unobvious difference between the claimed products and the products of the prior art (e.g. that the products of the prior art do not possess the same material structural and functional characteristics of the claimed product). See *in re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977). It is incumbent upon the applicant to provide evidence or comparative data to the contrary.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Tamura *et al.*, concerning a conjugate of hyaluronic acid and a therapeutic agent, such as non-steroidal anti-inflammatory drugs, for treatment of joint diseases, with the teachings of Miyamoto *et al.*, regarding glycosaminoglycans derivatives containing a carboxylic acid group, such as hyaluronic acid, which can be covalently bonded to a diamino spacer for further conjugation to peptides, proteins and other drugs. Since Tamura *et al.* teach the conjugation of hyaluronic acid to non-steroidal anti-inflammatory drugs, such as diclofenac, via a 1,2-diaminobutane spacer, and Miyamoto *et al.* teach that H_2N-$(CH_2)_n$-NH_2 wherein n is preferably 2-18 can be used as a spacer for conjugation of a glycosaminoglycan, such

as hyaluronic acid, to a protein, peptide or drug, it would have been *prima facie* obvious for one of ordinary skill in the art to substitute the spacers disclosed by Miyamoto *et al.* with the spacers disclosed by Tamura *et al.* One would have been motivated to make the substitution as it is expected that such a substitution would yield a predictable result. Furthermore, one would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Miyamoto *et al.*, that conjugation of a peptide, protein or drug to a glycosaminoglycan, such as hyaluronic acid, improves the stability of the peptide, protein or drug when it is in the living body (paragraph 0002).

It is noted that the Tamura *et al.* and Miyamoto *et al.* references do not explicitly teach sterilization of the conjugates through a filter, as indicated in claim 18. However, Miyamoto *et al.* explicitly teach filtration of their conjugates through a 0.22 micron filter (paragraph 0039 and 0042). One of ordinary skill in the art is well aware that filtration through of filter of that pore size is one method of sterilization.

With respect to the art rejection above, it is further noted that the references do not teach a kit which comprises the hyaluronic acid derivative solution in an injector or syringe, as indicated in instant claims 25-27. However, Tamura *et al.* explicitly teach that the hyaluronic acid conjugate with a non-steroidal anti-inflammatory drug can be used for treatment of osteoarthritis and rheumatoid arthritis by administering the conjugate intraarticularly as an injection. Thus, as all of the reagents and supplies used for administration are readily available and known to be used in the intraarticular treatment of arthritis, it would have been *prima facie* obvious for one of ordinary skill in the art to prepare everything into a kit ready for a practitioner to administer to a patient,

thereby minimizing the number of manipulative steps necessary by the practitioner which would minimize the possibility of contamination during preparation of the drug for administration. Furthermore, kits are regarded as a composition with a set of instructions. Where the only difference between a prior art product and a claimed product is printed matter that is not functionally related to the product, the content of the printed matter will not distinguish the claimed product from the prior art. *In re Ngai*, 367 F.3d 1336, 1339, 70 USPQ2d 1862, 1864 (Fed. Cir. 2004).

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shaojia Anna Jiang/
Supervisory Patent Examiner, Art Unit 1623

/SCARLETT GOON/
Examiner
Art Unit 1623